Movement Disorders
Vol. 25, No. 13, 2010, pp. 2203–2210

Risk and Learning in Impulsive and Nonimpulsive Patients With Parkinson's Disease

Atbin Djamshidian, MD,[1,2] Ashwani Jha, MBChB,[3] Sean S. O'Sullivan, MRCPI,[1] Laura Silveira-Moriyama, MD, PhD,[1] Clare Jacobson, MSc,[4] Peter Brown, MD, MRCP,[3] Andrew Lees, FMedAcadSci,[1] and Bruno B. Averbeck PhD[3]*

[1]*Department of Molecular Neuroscience and Reta Lila Weston Institute of Neurological Studies, UCL Institute of Neurology, London, United Kingdom*
[2]*2nd Neurological Department, General Hospital Hietzing with Neurological Center Rosenhuegel, Vienna, Austria*
[3]*Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, UCL, London, United Kingdom*
[4]*Department of Neuropsychology, Institute of Neurology, UCL, London, United Kingdom*

Abstract: Relatively little is known about the interaction between behavioral changes, medication, and cognitive function in Parkinson's disease (PD). We examined working memory, learning and risk aversion in PD patients with and without impulsive or compulsive behavior (ICB) and compared the results with those in a group of age-matched control subjects. Parkinson patients with PD+ICB had poorer working memory performance than either controls or PD patients without ICB. PD+ICB patients also showed decreased learning from negative feedback and increased learning from positive feedback in off compared with on dopaminergic medication. This interaction between medication status and learning was the opposite of that found in the PD patients without a diagnosis of ICB. Finally, the PD group showed increased risk preference on medication relative to controls, and the subgroup of PD+ICB patients with pathological gambling were overall more risk prone than the PD group. Thus, medication status and an impulsive behavioral diagnosis differentially affect several behaviors in PD. © 2010 Movement Disorder Society

Key words: Parkinson's disease; impulse control disorder; risk and learning; memory

The relationship between dopamine levels and cognitive function in Parkinson's disease (PD) has been the subject of much interest,[1,2] but there has been less work examining the interaction between behavioral changes and cognition.[3] Dopaminergic medication is effective in treating the motor symptoms of PD but can lead to impulsive or compulsive behaviors (ICB) in a minority of patients.[4] These behaviors include pathological gambling (PG), hypersexuality, compulsive shopping, binge eating, punding, and compulsive overuse of levodopa (dopamine dysregulation syndrome).[4–6] Risk factors for the development of ICBs include male sex, young age at onset, high novelty seeking personalities, and history of addiction.[7]

In early PD, there is greater dopamine depletion in the dorsal striatum than in the ventral striatum.[8] Clinically, effective dopamine replacement in the dorsal striatum can overstimulate the relatively intact ventral striatum and lead to undesirable cognitive changes.[9] A number of behavioral correlates of medication status (off *vs.* on) have been documented. For example, PD patients are more sensitive to negative feedback and less sensitive to positive feedback when in off medication, whereas they show the opposite behavior on medication.[10] Furthermore, PD patients on higher L-dopa doses are more impulsive than controls.[11]

PATIENTS AND METHODS

Patients were recruited from a database of attendees at the National Hospital for Neurology and Neurosur-

Additional Supporting Information may be found in the online version of this article.

*Correspondence to: Dr. Bruno B. Averbeck, Laboratory of Neuropsychology, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892. E-mail: averbeckbb@mail.nih.gov

Potential conflict of interest: The authors declare no financial or other conflict of interest.

Received 11 November 2009; Revised 18 January 2010; Accepted 15 April 2010

Published online 18 August 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23247

gery, Queen Square, London, United Kingdom. Controls were usually recruited from amongst the patients' partners. Written informed consent was obtained from all participants. Patients were asked to take no anti-Parkinsonian medication overnight (12–18 hours) and were tested first between 8.00 AM and 9.00 AM before their morning medication. Patients then took their first L-dopa dose, and the tests were repeated 50 minutes later. The therapeutic motor response to L-dopa was assessed by UPDRS scores (Part 3) during "off" and "on" state. All patients had an excellent L-dopa response and had switched "on" at the second test. Levodopa equivalent units were calculated as described previously.[12] Testing was performed in the patient's homes using a laptop computer. Distractions were minimized, so that full attention could be devoted to the task. Controls were tested following a similar sequence, *i.e.*, they were tested once and then retested after 50 minutes but received no medication. To ensure that patients did not fatigue during the study, a self-rating questionnaire to monitor interest, attentiveness, and alertness was obtained before and after medication (see Supporting Information).

The first task was a forward and backward digit span test[13] to assess working memory (WM). The second task was an associative learning task in which subjects were required, in each of four blocks of trials, to learn which of two stimuli was most often rewarded.[14,15] In each trial, they selected one stimulus and were then told whether or not they "won" on that trial. Winning probabilities for the two stimuli (75%/25% and 65%/35% were used in different blocks) were constant throughout each block and balanced across stimuli across blocks (see Supporting Information for additional details). The final task was a gambling task, which was designed to probe the risk aversion of the subjects and programmed to match the description given of the task in Huettel et al.[16] In each trial subjects, were given a choice between two gambles with varying levels of risk. Subjects chose one gamble and were then told of the outcome (see Supporting Information for additional details).

Mixed-effects ANOVA models were fit to behavioral variables. Subject was treated as a random effect nested under group. Group and session were treated as fixed effects, and session was treated as a within-subject effect. All post hoc comparisons were corrected using Tukey's HSD test. For the WM task, the raw WM scores were converted into scaled scores according to published normative tables.[13] For the learning and risk tasks, ANOVAs were carried out on parameters from computational models fit to the behavioral data of individual subjects (see Supporting Information Methods for details of the models). For the learning task, we fit two parameters, which were treated as within subject factors. The first parameter characterized the amount that positive feedback, after selecting one of the stimuli, affected future decisions, and the second parameter characterized the same for negative feedback. For the risk task, we fit two parameters. The first (c from Supporting Information Methods) characterized how much the subjects valued large *vs*. small rewards. Larger positive values of this parameter imply that subjects prefer small, sure rewards to large rewards with a lower probability. Thus, this parameter characterizes the amount of risk to which subjects are prone. The second parameter (d from Supporting Information Methods) characterized whether subjects became more risky following a win. For the risk analysis, the ANOVAs were carried out separately for each parameter.

RESULTS

Demographic Characteristics

All patients fulfilled the Queen Square Brain Bank criteria for PD[17] and were taking L-dopa (Table 1). Twelve patients with idiopathic PD without ICB (3 of 12 female) and 18 PD patients with ICBs (5 of 18 female) were compared against 22 healthy controls (10 of 22 female). All PD+ICB patients had at least 2 ICB. PD+ICB patients had an earlier disease onset ($t_{28} = 2.1$, $P = 0.04$). The average time lag between the diagnosis of an ICB and the testing was 5.6 months. Twelve PD+ICB patients were included in a previous study.[18]

All patients were screened for subclasses of ICBs (Table 1). Nine PD+ICB were tested during reduction of their dopamine agonist medication; seven patients had already reduced their dopamine agonist medication, which had improved their impulsive behavior. At the time of testing, they still fulfilled the criteria of ICB with the exception of two patients, who had fulfilled these criteria within the previous 12 months. All patients with ICBs developed their behavioral abnormalities as a direct result of medication.

An ANOVA to test difference between ages in the three groups just failed to reach significance ($F_{2,49} = 3.2$, $P = 0.051$). Post hoc comparisons were not significant between the PD group *vs*. the control ($P = 0.07$) or PD+ICB group ($P = 0.098$). There was no significant difference in the morning ($t_{28} = 1$, $P = 0.3$) and daily L-dopa dose between the patient groups ($t_{28} = 0.9$, $P = 0.36$). The timing of the last dopaminergic medication was not significantly different between the patient groups ($t_{25} = 0.3$, $P = 0.2$). We assessed years

TABLE 1. *Subject demographics*

	Controls	PD	PD+ ICB	*P*
Participants in total (n)	22	12	18	
Age (yr)				
Currently	55 ± 3.0	63.6 ± 2.2	55 ± 2.1	0.051
At disease onset	–	50.9 ± 2.2	43.9 ± 2.1	0.04
Disease duration (yr)	–	12.7 ± 2.1	10.9 ± 1.2	0.8
Education (yr)	13.8 ± 0.7	14.2 ± 1.3	12.2 ± 0.9	>0.15
DDS	–	–	6	
Pathological gambling	–	–	10	
Hypersexuality	–	–	9	
Compulsive shopping	–	–	5	
Binge eating	–	–	7	
Kleptomania	–	–	1	
Punding	–		2	
Morning L-dopa dose (mg)	–	170 ± 21	185 ± 32	0.3
Total L-dopa dose (mg)	–	604 ± 73	752 ± 109	0.36
LEU dose (mg)	–	732 ± 203	971 ± 183	0.1
DA (patients)	–	7	9	0.89
MAO inhibitor (patients)	–	5	6	0.6
Entacapone (patients)	–	5	6	0.6
UPDRS OFF medication	–	24 ± 1.6	38 ± 3.4	0.002
UPDRS ON medication	–	13 ± 1.4	18 ± 2.2	0.12
Average improvement in UPDRS (%)		46	53	

All values are mean ± SEM. Pathological gambling assessed with DSM IV criteria, compulsive shopping assessed with McElroy *et al.*'s criteria,[35] hypersexuality assessed with questionnaire suggested by Voon *et al.*[36] and punding (see Table 1).

DDS, dopamine dysregulation syndrome; UPDRS, Unified Parkinson's Disease Rating Scale; LEU, L-dopa equivalent units; DA, dopamine agonist; NS, nonsignificant.

of education in 17 of 22 controls, 9 of 12 PD patients, and 14 of 18 ICB patients and found no significant difference ($F_{2,37} = 1.98$, $P = 0.15$).

Working Memory

The WM task showed a main effect of group ($F_{2,47} = 6.9$, $P = 0.002$) and task ($F_{1,131} = 16.0$, $P < 0.001$) and a significant interaction between these factors ($F_{2,131} = 3.3$, $P = 0.040$) but no effect of off *vs.* on ($F_{1,131} = 0.007$, $P = 0.9$). To examine these effects in more detail, two additional ANOVAs with post hoc comparisons were carried out, which revealed that the overall WM (digit forward + backward span) was significantly impaired in the PD+ ICB group compared with both the control ($P = 0.006$) and PD groups ($P = 0.014$), but there was no difference between the PD group and controls ($P = 1.00$; Fig. 1A). More specifi-

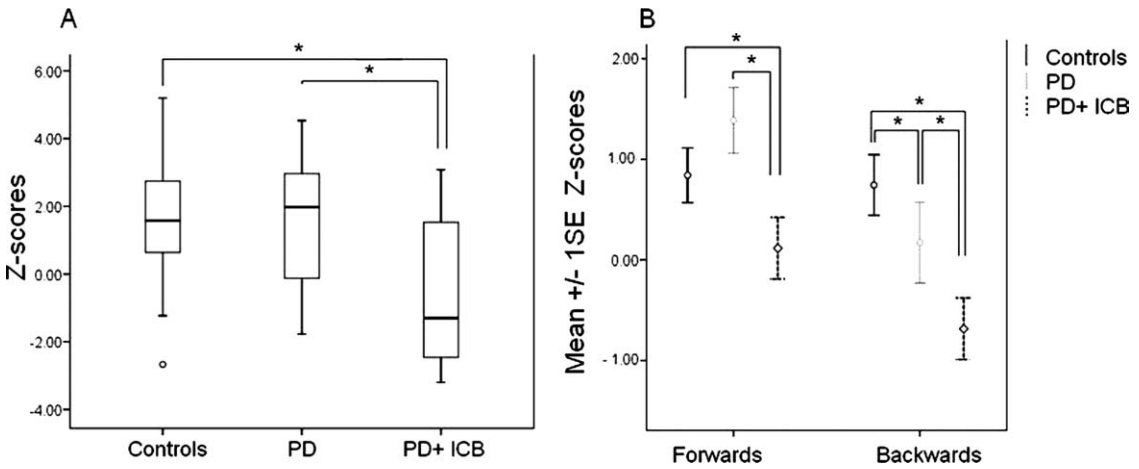

FIG. 1. A, Overall WM performance. Box plot showing the median (horizontal line) within a box containing the central 50% of the observations (*i.e.*, the upper and lower limits of the box are the 75th and the 25th percentiles) and extremes of the whiskers containing the central 95% of the ordered observations. Controls and PD without and with ICB. Outliner is shown as circle. B, WM between the three groups, split by tasks (forward-backward). Values are mean (± 1 SEM). Significant differences were labeled with "*" in both figures.

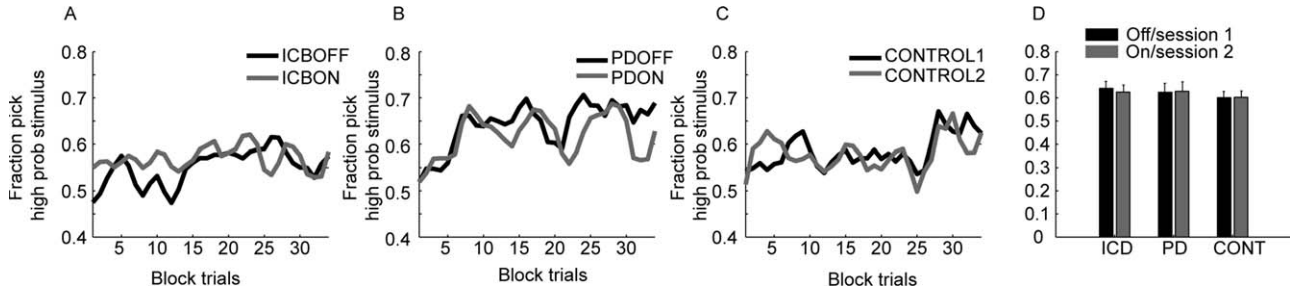

FIG. 2. Average learning referenced to the stimulus, which has the highest probability of being correct in the block. A, Learning rate for PD patients with ICB off and on medication. B, Learning rate for PD group off and on medication. C, Learning rate for control group, 1st and 2nd sessions. D, Average choices referenced to the stimulus, which is most probably best at each trial in the block. Error bars are ± 1 SEM.

cally, PD+ICB patients performed significantly worse on the forward task than the PD and control groups (both, $P < 0.001$) and also performed significantly worse on the backward task than the PD ($P = 0.01$) and control groups ($P < 0.001$). There were no significant differences between PD and controls in the forward task ($P = 0.09$), but the control group was significantly better than the PD group in the backward task ($P = 0.01$; Fig. 1B).

Learning Task

Overall, the number of times that subjects picked the most rewarded image was similar between on and off conditions (Fig. 2A–C). The feedback associated with each image was stochastic and could favor the image with a higher probability of being rewarded. We compared the choices of the subjects with an ideal observer which always made the optimal decision, given the feedback up to the current trial in each block [Eq. (3), Supporting Information). All subject groups (Fig. 2D) made the same choice as the ideal observer at above chance levels (ICBOFF, $t_{19} = 4.7$, $P < 0.001$; ICBON, $t_{19} = 4.1$, $P = 0.001$; PDOFF, $t_{11} = 3.2$, $P = 0.009$; PDON, $t_{11} = 3.1$, $P = 0.010$; CONTROL1, $t_{16} = 3.8$, $P = 0.002$; CONTROL2, $t_{16} = 3.8$, $P = 0.002$). A comparison of group and session in a mixed-model ANOVA showed no significant effect of group ($F_{2,46} = 1.17$, $P = 0.319$), session ($F_{1,46} = 0.14$, $P = 0.71$), or interaction ($F_{2,46} = 0.15$, $P = 0.857$).

Next, we compared learning from positive and negative feedback across groups. When all three groups were compared, there was a significant effect of valence ($F_{1,46} = 65.9$, $P < 0.001$), but there were no other significant effects. Subsequently, we carried out an ANOVA directly comparing the PD and ICB groups, excluding the control group. In these groups, there was a main effect of valence ($F_{1,30} = 83.07$, $P < 0.001$) but no other main effects or 2-way interactions. There was, however, a 3-way interaction between valence, group, and session ($F_{1,30} = 6.55$, $P = 0.016$; Fig. 3D). We followed up this result with separate ANOVAs in the two individual groups and found a significant interaction between session and type of feedback for the PD+ICB group (Fig. 3A; $F_{1,19} = 4.8$, $P = 0.041$), as well as a significant main effect of feedback valence ($F_{1,19} = 12.43$, $P = 0.002$). The PD group showed a main effect of feedback valence (Fig. 3B; $F_{1,11} = 14.6$, $P = 0.003$) but no inter-

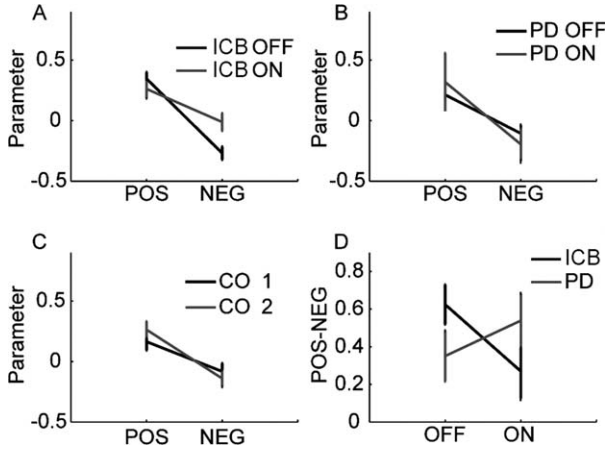

FIG. 3. Learning from positive and negative feedback for patients with ICB, PD, and control groups. All values are mean (±1 SEM). A, Learning from positive and negative feedback on and off medication. B, Same as A for non-ICB PD. C, Learning from positive and negative feedback in first and second test session in control subjects. D, Within-subject difference in learning from positive *vs.* negative feedback for PD patients with ICB *vs.* non-ICB patients off and on medication.

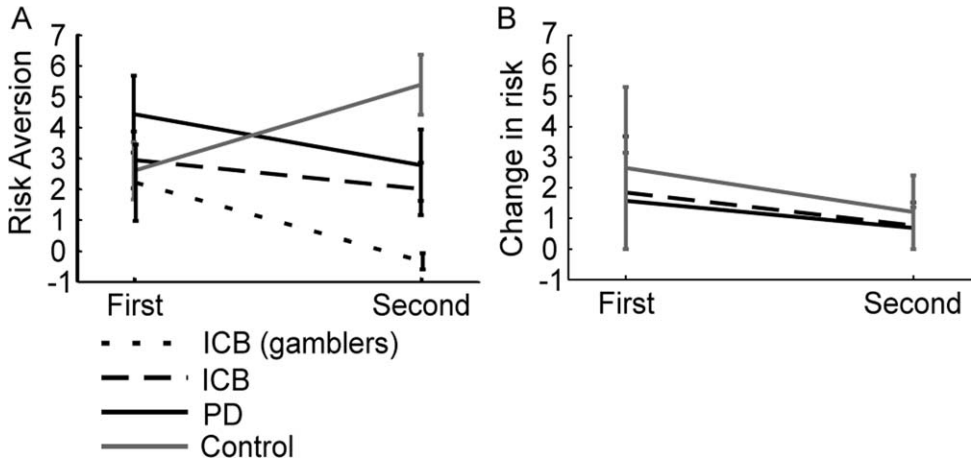

FIG. 4. Risk preference. All values are mean (±1 SEM) A, Risk preference by group on (2nd trial for patients) and off (1st trial for patients) dopamine medication. This is parameter *c* from the risk model described in the Supporting Information. B, Change in risk preference following a win: parameter *d* from the risk model described in the Supporting Information.

action between session and valence ($F_{1,11} = 2.83$, p = 0.121). Finally, it is important to point out that although learning rates were negative in some cases, these are relative to a baseline of 0.5 (Methods in Supporting Information); therefore, learning from both positive and negative feedback are greater than zero and larger for positive than negative feedback, as they should be.

Risk Task

We modeled two effects in the risk task. The first was an overall risk aversion term (parameter *c*), and the second was whether subjects became more or less risk averse if they won in the previous trial (parameter *d*). First, controls showed an increase in risk aversion in the second test session, whereas both patient groups showed an increase in risk preference in the second session relative to the first session (Fig. 4A). An ANOVA that included all three groups had no significant main effects of group or session but did show a significant interaction between group and session ($F_{2,48} = 4.2$, $P = 0.021$). Post hoc comparisons of the difference of the sessions showed that the controls were significantly different than the PD subjects ($P = 0.036$) but did not differ significantly from the ICB group (p = 0.052). Next, we carried out an ANOVA on only the PD and PD+ICB groups and found no significant differences. However, when the PD group was compared with the subset of ICB patients that had PG (n = 10, ICB gamblers, Fig. 4A), there was a main effect of group ($F_{1,21} = 7.9$, $P = 0.011$) and session ($F_{1,21} = 4.77$, $P = 0.040$). We also analyzed whether subjects became more risk prone after a win. An ANOVA across all three groups showed a main effect of session ($F_{1,48} = 5.3$, $P = 0.030$) but no other main effects or interactions (Fig. 4B). When the analysis was restricted to PD and PD+ICB groups or the PD and PD+ICB gamblers, there were no significant main effects or interactions.

DISCUSSION

WM was significantly reduced in PD+ICB patients compared with the PD and control groups. PD patients showed impairment in the digit backward span test compared with controls, consistent with a recent publication.[19] We did not find an improvement of WM after medication. Previous studies have shown that WM is reduced in impulsive patients with attention deficit/hyperactivity disorder and healthy controls who scored highly on an impulsivity questionnaire. These subjects had lower total striatal dopamine levels, which seem to be associated with lower WM capacity.[20,21] Other studies have shown impaired spatial memory in patients with impulse control disorders.[22]

We found that PD+ICB patients showed increased learning from positive *vs*. negative feedback off medication compared with on medication, whereas non-ICB patients showed a trend toward the previously described learning effects.[10] Furthermore, the group by session by valence interaction was significant, such that these learning effects were significantly complimentary. These effects appear to be inconsistent with recently reported results on impulsive patients with PD.[23] However, there are fundamental differences between their approach and ours that may account for these discrep-

ancies. They used interleaved win (*i.e.*, win \$10/lose \$0) and loss (*i.e.*, lose \$10/win \$0) conditions and fitted one learning rate parameter to the win condition and one to the loss condition. In our approach, we fitted separate parameters to positive and negative outcomes within a single condition. Thus, we would have fit separate parameters to the win \$10 and the lose \$0 outcomes within the win condition, and correspondingly in their loss condition, whereas they fit a single parameter. It is not clear, therefore, whether the positive or negative outcomes are driving the learning rate in each of their conditions and to what extent. Thus, it is difficult to directly compare both the studies, which may account for the differences we have found. We also use a slightly different modeling approach. We show in the Supporting Information that our modeling approach works better on our data and that it provides roughly consistent estimates of learning when compared with the modeling approach used previously.[23]

It is important to consider the limitations of our study. First, we used unbalanced gains (10 pence) and losses (5 pence) in our learning paradigm; so, it might be the differential magnitude that the PD+ICB patients are sensitive to. However, we think it is unlikely that differential sensitivity to reward magnitude could underlie the group differences with respect to the effects of medication, as we found that dopaminergic medication status affected risk preference (which measures sensitivity to reward magnitude) in the same way in PD and PD+ICB patients and, yet, medication had contrasting effects in the learning task. The valence effect we saw across groups, however, could be due to the unbalanced gains and losses, as all groups appeared to learn more from gains than losses. Second, to minimize the effects of our study on patients, data collection was performed in one morning in fixed order; off medication then on medication. Thus, practice effects cannot be separated from the on medication effects. Accordingly, we also ran the control subjects twice to attempt to control for practice effects through the morning. However, the latter does not negate the possibility of an interaction between practice and disease, so that practice effects may have been different in patients. In the light of the effects demonstrated in the current study, we have embarked on a follow-up study in which the order of drug states is counterbalanced across patients (and losses and gains are balanced).

PET studies of dopamine release have shown that dopamine medication leads to elevated ventral striatal dopamine release in PD+ICB patients relative to PD patients without ICB.[24,25] These observations and our results are consistent with the hypothesis that PD+ICB patients have elevated baseline dopamine levels in the ventral striatum and that dopaminergic medication increases the levels further, reducing learning from positive feedback. This might be explained by the "inverted U" shape hypothesis[26,27] where the ability to pick the rewarded stimulus might be impaired when PD+ICB subjects are pushed off the upper end of the curve by their medication.

The risk task was designed to test the hypothesis that patients with ICB are more risk prone than non-ICB patients.[28] Previous authors have described the premorbid Parkinsonian personality as one characterized by caution, risk aversion, and anhedonia.[29] In contrast PD+ICB patients have a behavioral profile characterized by increased impulsiveness or novelty seeking[28] similar to subjects prone to substance abuse and behavioral addictions.[30] Overall, PD+ICB patients showed a trend to be more risk prone relative to normal PD, which did not reach significance. However, PD+ICB patients who had PG were significantly more risk prone than the PD group. A tendency toward risky behavior has also been found in pathological gamblers.[31] Furthermore, dopaminergic medication led to increased risk preference in the PD patients relative to the healthy controls and just missed significance in ICB patients *vs.* controls. This is particularly interesting because risk taking decreases with age[32] and there was a trend for the normal PD group to be older than both groups. These findings are consistent with two recently published studies, which showed that dopamine agonists lead to increased novelty seeking and a reduction in negative feedback learning.[33,34]

We have demonstrated differences in learning between PD patients with and without ICBs. These differences could be explained by higher ventral striatal dopamine levels in PD+ICB patients. In addition, PD patients with PG were more risk prone compared with normal PD patients and healthy controls. These findings may have therapeutic and clinical implications. The reduction in the overall anti-Parkinsonian medication with positive reinforcement of nonimpulsive behavior is likely to be more beneficial than aversion therapy in PD+ICB patients.

Acknowledgments: This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. We thank Karen Shaw for advice with the ethics amendment for this study. We also thank all patients and their partners who participated on this study.

Author Roles: 1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing

of the first draft, B. Review and Critique; Atbin Djamshidian: 1, 2, 3; Ashwani Jha: 1B, 2A, 2C, 3B; Sean S. O'Sullivan: 1A, 1B, 2C, 3B; Laura Silveira-Moriyama: 2, 3B; Clare Jacobson: 2A, 2B, 3B; Peter Brown: 1A, 1B, 2A, 2C, 3B; Andrew Lees: 1A, 2C, 3B; Bruno B. Averbeck: 1A, 1B, 2, 3B.

Financial Disclosures:Stock Ownership in medically-related fields: Atbin Djamshidian, Ashwani Jha, Sean O'Sullivan, Laura Silveira-Moriyama; Clare Jacobson, Peter Brown, Andrew Lees, Bruno Averbeck—none; Consultancies: Atbin Djamshidian, Ashwani Jha, Sean O'Sullivan, Laura Silveira-Moriyama; Clare Jacobson, Peter Brown, Andrew Lees, Bruno Averbeck—none; Advisory Boards: Atbin Djamshidian, Ashwani Jha, Sean O'Sullivan, Laura Silveira-Moriyama; Clare Jacobson—none, Peter Brown—Medtronic, Andrew Lees—Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergan; Orion; Bruno Averbeck—none; Partnerships: Atbin Djamshidian, Ashwani Jha, Sean O'Sullivan, Laura Silveira-Moriyama; Clare Jacobson, Peter Brown, Andrew Lees, Bruno Averbeck—none; Honoraria: Atbin Djamshidian—none, Ashwani Jha—none, Sean O'Sullivan—Britannia Pharmaceuticals, Laura Silveira-Moriyama—Britannia Pharmaceuticals; Clare Jacobson—none, Peter Brown—Medtronic, Andrew Lees—Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergan; Orion; Bruno Averbeck—none; Grants: Atbin Djamshidian—none, Ashwani Jha—UK Parkinson's Disease Society; Sean O'Sullivan—UK Parkinson's Disease Society; Laura Silveira-Moriyama—none; Clare Jacobson—none; Peter Brown—none; Andrew Lees—PSP Association Weston Trust, The Reta Lila Howard Foundation; Bruno Averbeck—Wellcome, Intramural research program of the National Institute of Mental Health; Intellectual Property Rights: Atbin Djamshidian, Ashwani Jha, Sean O'Sullivan, Laura Silveira-Moriyama; Clare Jacobson, Peter Brown, Andrew Lees, Bruno Averbeck—none; Expert Testimony: Atbin Djamshidian, Ashwani Jha, Sean O'Sullivan, Laura Silveira-Moriyama; Clare Jacobson, Peter Brown, Andrew Lees, Bruno Averbeck—none; Employment: Atbin Djamshidian—Reta Lila Weston Foundation, Ashwani Jha—UCL/UCLH, Sean O'Sullivan—Barts and the London NHS Trust, UK; Laura Silveira-Moriyama—Reta Lila Weston Foundation; Clare Jacobson—UCL/UCLH, Peter Brown—UCL/UCLH, Andrew Lees—UCL/UCLH, Bruno Averbeck—UCL/UCLH; Contracts: Atbin Djamshidian, Ashwani Jha, Sean O'Sullivan, Laura Silveira-Moriyama; Clare Jacobson, Peter Brown, Andrew Lees, Bruno Averbeck—none; Royalties: Atbin Djamshidian, Ashwani Jha, Sean O'Sullivan, Laura Silveira-Moriyama; Clare Jacobson, Peter Brown, Andrew Lees, Bruno Averbeck—none; Others: Atbin Djamshidian, Ashwani Jha, Sean O'Sullivan, Laura Silveira-Moriyama; Clare Jacobson, Peter Brown, Andrew Lees, Bruno Averbeck—none.

REFERENCES

1. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006;30:1–23.
2. Lewis SJ, Slabosz A, Robbins TW, Barker RA, Owen AM. Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. Neuropsychologia 2005;43:823–832.
3. Dagher A, Robbins TW. Personality, addiction, dopamine: insights from Parkinson's disease. Neuron 2009;61:502–510.
4. Lawrence AD, Evans AH, Lees AJ. Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? Lancet Neurol 2003;2:595–604.
5. Weintraub D, Potenza MN. Impulse control disorders in Parkinson's disease. Curr Neurol Neurosci Rep 2006;6:302–306.
6. Brewer JA, Potenza MN. The neurobiology and genetics of impulse control disorders: relationships to drug addictions. Biochem Pharmacol 2008;75:63–75.
7. Voon V, Hassan K, Zurowski M, et al. Prospective prevalence of pathologic gambling and medication association in Parkinson disease. Neurology 2006;66:1750–1752.
8. Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. N Engl J Med 1988;318:876–880.
9. Gotham AM, Brown RG, Marsden CD. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain 1988;111(Pt 2):299–321.
10. Frank MJ, Seeberger LC, O'Reilly R C. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 2004; 306:1940–1943.
11. Torta DM, Castelli L, Zibetti M, Lopiano L, Geminiani G. On the role of dopamine replacement therapy in decision-making, working memory, and reward in Parkinson's disease: does the therapy-dose matter? Brain Cogn 2009;71:84–91.
12. Evans AH, Katzenschlager R, Paviour D, et al. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. Mov Disord 2004;19:397–405.
13. Wechsler D. Wechsler adult intelligence scale, Third ed. San Antonio: The Psychological Corporation; 1997.
14. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 2006;442:1042–1045.
15. Averbeck BB, Duchaine B. Integration of social and utilitarian factors in decision making. Emotion 2009;9:599–608.
16. Huettel SA, Stowe CJ, Gordon EM, Warner BT, Platt ML. Neural signatures of economic preferences for risk and ambiguity. Neuron 2006;49:765–775.
17. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745–752.
18. O'Sullivan S, Djamshidian A, Evans A, Loane C, Lees AJ, Lawrence AD. Excessive hoarding in Parkinson's disease. Mov Dis 2010;25:1026–1033.
19. Mamikonyan E, Moberg PJ, Siderowf A, et al. Mild cognitive impairment is common in Parkinson's disease patients with normal Mini-Mental State Examination (MMSE) scores. Parkinsonism Relat Disord 2009;15:226–231.
20. Cools R, Sheridan M, Jacobs E, D'Esposito M. Impulsive personality predicts dopamine-dependent changes in frontostriatal activity during component processes of working memory. J Neurosci 2007;27:5506–5514.
21. Frank MJ, Santamaria A, O'Reilly RC, Willcutt E. Testing computational models of dopamine and noradrenaline dysfunction in attention deficit/hyperactivity disorder. Neuropsychopharmacology 2007;32:1583–1599.
22. Voon V, Reynolds B, Brezing C, et al. Impulsive choice and response in dopamine agonist-related impulse control behaviors. Psychopharmacology (Berl) 2010;207:645–659.
23. Voon V, Pessiglione M, Brezing C, et al. Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. Neuron 2010;65:135–142.
24. Evans AH, Pavese N, Lawrence AD, et al. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. Ann Neurol 2006;59:852–858.
25. Steeves TD, Miyasaki J, Zurowski M, et al. Increased striatal dopamine release in Parkinsonian patients with pathological gam-

bling: a [11C] raclopride PET study. Brain 2009;132(Pt 5):1376–1385.
26. Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia 2003;41:1431–1441.
27. Williams GV, Goldman-Rakic PS. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature 1995;376:572–575.
28. Voon V, Thomsen T, Miyasaki JM, et al. Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. Arch Neurol 2007;64:212–216.
29. Todes CJ, Lees AJ. The pre-morbid personality of patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1985;48:97–100.
30. Sher KJ, Bartholow BD, Wood MD. Personality and substance use disorders: a prospective study. J Consult Clin Psychol 2000;68:818–829.
31. Brand M, Kalbe E, Labudda K, Fujiwara E, Kessler J, Markowitsch HJ. Decision-making impairments in patients with pathological gambling. Psychiatry Res 2005;133:91–99.
32. Deakin J, Aitken M, Robbins T, Sahakian BJ. Risk taking during decision-making in normal volunteers changes with age. J Int Neuropsychol Soc 2004;10:590–598.
33. Abler B, Hahlbrock R, Unrath A, Gron G, Kassubek J. At-risk for pathological gambling: imaging neural reward processing under chronic dopamine agonists. Brain 2009;132(Pt 9):2396–2402.
34. Bodi N, Keri S, Nagy H, et al. Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. Brain 2009;132(Pt 9):2385–2395.
35. McElroy SL, Keck PE Jr, Pope HG Jr, Smith JM, Strakowski SM. Compulsive buying: a report of 20 cases. J Clin Psychiatry 1994;55:242–248.
36. Voon V, Hassan K, Zurowski M, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology 2006;67:1254–1257.